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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/576,509	04/19/2006	Philippe Chatellard	ARS.127	6271
23557 7590 03/12/2010 SALIWANCHIK LLOYD & SALIWANCHIK A PROFESSIONAL ASSOCIATION PO Box 142950 GAINESVILLE, FL 32614				
EXAMINER KELLY, ROBERT M				
ART UNIT		PAPER NUMBER		
1633				
NOTIFICATION DATE		DELIVERY MODE		
03/12/2010		ELECTRONIC		

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

euspto@slspatents.com

### Office Action Summary

**Application No.**

10/576,509

**Applicant(s)**

CHATELLARD ET AL.

**Examiner**

ROBERT M. KELLY

**Art Unit**

1633

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 17 December 2009.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 52-74 and 76 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 52-74 and 76 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-8508)  
Paper No(s)/Mail Date \_\_\_\_\_

- 4) ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date \_\_\_\_\_
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: \_\_\_\_\_

**DETAILED ACTION**

Applicant's amendment and argument of 12/17/09 are entered.

Claims 54, 56, 59-64, 73, and 74 are presently amended.

Claim 76 is newly added.

Claims 52-74 and 76 are presently pending and considered.

***Claim Rejections - 35 USC § 112 - clarity***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

While previous rejections are withdrawn (i.e., Claims 55, 56, 63-65, 67, and 68), due to the amendments, the following new rejections are made:

In light of the amendments, all rejections to Claims 54, 56-68, 73, and 74 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, are withdrawn.

To wit, the amendments overcome the bases of clarity previously rejected.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 52-55, 57, 58, 62-64, and 69-73 remain rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 6,395,549 to Tuan, et al., Recillas-Targa, et al. (2002) Proceedings of the National Academy of Sciences, USA, 99(10) 6883-88), Chung, et al. (1997) Proceedings of the National Academy of Sciences, USA, 94: 575-80, and U.S. Patent No. 6,432,700 to Henderson, et al, for reasons of record.

Tuan teaches integrating vectors comprising enhancers, insulators, and promoters to drive the expression of any gene of interest in animal cells (ABSTRACT). Further, it is taught to use barrier-function sequences to isolate the integrated vector from position effects in the chromatin to avoid silencing (e.g., Detailed Description of the Invention, paragraph 5). Hence, Tuan teaches that it is known in the Art to place barrier-function sequences on both sides of an integrating vector in order to protect it from silencing, and this can be used for the expression of desired transgenes. Further Tuan teaches the use of GFP coding sequences as a reporter for expression (e.g., paragraph preceding "Constructs and Vectors), and further to link the expression of such GFP to hCMV to obtain expression in cells (e.g., Figure 8), as it is well known that such promoters are widely active in many cell types (absent reason to believe otherwise, this is hCMV-IE1, as such is the standard utilized in the Art for constitutive expression). Hence, the Artisan would know that the use of a GFP coding sequence would allow quick identification of transformed cells, as is standard in the Art to identify the transformed and expressing cells.

Recillas-Targa teaches that the position protection effect of the chicken beta-globin insulator is located in a larger region encompassed by Applicant's SEQ ID NO: 1 (e.g., Figure 1), and is severable from the enhancer blocking activity (e.g., TITLE). Further, Recillas-Targa

teaches that it is normal to utilize two copies of the position-effect on both sides of the vector provide for good isolation from position effects (e.g., p. 6885, col. 2, paragraph 3). Lastly, Recillas-Targa teaches minimization of domain sizes (e.g., whole article).

Chung teaches that the same insulator as Recillas-Targa is active in mammalian cells (e.g., p. 576, col. 2, paragraph 2).

Henderson teaches that it is optimal to minimize the size of the other components of the vector, in order to make more room for transgenes which are to be expressed (e.g., col. 17, paragraph 1).

Further, Official Notice is provided that polyA sequences are known in the Art for transcriptional processing, and typically used in the Art.

Hence, from this, the Artisan would be motivated to make an integrating vector, comprising two copies of SEQ ID NO 1 on each end of the integrating vector, with the normally-present base that Applicant has removed from the sequence, and further to comprise the CMV promoter driving expression of GFP. The Artisan would be so-motivated to provide the minimal sequence of the beta-globin barrier sequence of Recillas-Targa, and do so to express proteins in mammalian cells, as is taught in Chung. In addition, there is a reasonable expectation of success, as the use of such barriers was known, the methods of minimization were known, and the methods of utilizing such to express proteins from integrated vectors was known.

However, such, in itself, does not make obvious the further deletion of the base which Applicant's SEQ ID NO: 1 is missing, from that of the known sequence of the chicken beta globin insulator/barrier sequence.

On the other hand, it is clear that the Artisan knew that the important sequences for the barrier functions were those regions that did not bind proteins (e.g., Recillas-Targa, DISCUSSION), and that intervening sequences were not known to be important. Moreover, Applicant's deleted base is within the intervening sequences (e.g., Chung, FIGURE 3, line 5 of the sequence, the penultimate "C" in such line, determined by comparison to Applicant's specification, FIGURE 1).

Hence, it would be obvious to further delete the "C" between the binding regions. The Artisan would have done so to further minimize the size the barrier region. Further the Artisan would have expected success, as such region was not bound by any proteins which cause the barrier effect.

Therefore, the Artisan would make these integrating vectors and transform mammalian cells with such vectors to express transgenes, including GFP for identification of those cells expressing the transgene. The Artisan would have expected success, as the methods were known in the Art.

***Response to Argument – 103 – Tuan/Recillas-Targa/Chung/Henderson***

Applicant's arguments of 12/17/09 have been fully considered but are not found persuasive.

Applicant argues that the Examiner is incorrect in the rejection, and this is because, quoting KSR "it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way claimed new invention does" (p. 9, penultimate paragraph).

Such is not persuasive. First, the quote itself is flawed, stating “it can be relevant ...”, which necessarily means it does not have to be so. Second, a motivation is found, as is clearly stated in the action: to decrease the size of the barrier region, as Applicant has quoted in their response. The question here is really one of whether or not Applicant's choice of specific deletion contributes to an advancement of the useful arts (here, cellular gene expression of transgenes). Clearly, there is no unexpected property, and there is no Art on the record that doubts whether it would work in the first place. There is even art, as cited, that suggests deletions, as well as that the non-protein-binding regions may be deleted. Applicant's argument is to choose a single base within the sequence, which admittedly is long, and use such to find non-obviousness. However, this is wrong, because the Art already recognized that deletions in these regions were allowed. Moreover, motivation is found to decrease the size of the insulator. With regard to averments that the prior art did not suggest the desirability of the [specific] modification, it is not needed. If such was needed, we would always see a laundry list of a huge array of modifications which are disallowed or allowed, in every case where there are possible modifications. It is much more expedient in science to explain the overall reasoning why regions may be deleted, and as above, such is made clear, as shown in the Art.

Applicant argues that the Examiners analysis, utilizing Henderson and Recillas-Targa teaches large swaths of DNA should be removed to make room for genes, and that therefore, their specific single-base deletion is not-obvious, and therefore, implying an advancement to the Art, because they have taught that single base deletions may be had (pp. 10-11, paragraph bridging).

Such is not persuasive. The deletion is motivated to reduce size, and all reductions in size are therefore obvious, unless the Art teaches against it, or there is no reason to believe it would work in the Art. In the instant case, Recillas-Targa teaches that the region is one that does not bind to proteins and was not known in the Art to be important. Moreover, there need not only be deletions in the specific sequence, but it must be considered with all other sequences which are placed in the vector. The analysis that all deletions must come from the insulator is flawed. Moreover, the analysis that a single nucleotide is useless to delete is wrong, because minimization in size is made of many minimizations to meet the desired size for the vector. Simply put, in the end, Recillas-Targa makes clear that the regions is not known to be important, and the deletion therefore is obvious as one of design choice.

### *Claim Rejections - 35 USC § 103*

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 52-59, 62-67, and 69-74 remain rejected, and Claim 76 is newly rejected, under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 6,395,549 to Tuan, et al., Recillas-Targa, et al. (2002) Proceedings of the National Academy of Sciences, USA, 99(10) 6883-88), Chung, et al. (1997) Proceedings of the National Academy of Sciences, USA, 94: 575-80, and U.S. Patent No. 6,432,700 to Henderson, et al. as applied to claims 52-55, 57, 58, 62-64, and 69-73 above, and further in view of Perlman, et al. (2003) The Journal of Clinical Endocrinology &



Metabolism, 88(7): 3227-35 and Aldrich, et al. (1998) Cytotechnology, 28: 9-17, for reasons of record.

As shown above, the Art teaches various claims, but does not teach the polypeptide of interest being FSH alpha and beta subunits, or the use of CHO cells, bicistronic vectors and the question of isolation of the protein has not been addressed.

On the other hand, Perlman teaches that CHO cells can be used to express FSH from vectors comprising the alpha and beta subunits (e.g., p. 3228, col. 1).

Aldrich teaches the use of bicistronic vectors for expression, which provide for reducing the time required to develop cell pools for protein expression (e.g., ABSTRACT).

Moreover, the Artisan would isolate the FSH for use (Official Notice).

Hence, it would be further obvious to transform CHO cells with such vectors carrying the alpha and beta subunits of FSH in a bicistronic vector. The Artisan would be motivated to do so in order to express and isolate FSH from the cells with reduced time to develop cell pools for protein expression. Moreover, the Artisan would have a reasonable expectation of success, as the cells were already known for expression of FSH and isolation techniques are known in the Art.

***Response to Argument – 103 – Tuan/Recillas-Targa/Chung/Henderson/Perlman/Aldrich***

Applicant's arguments rely on the base argument above, and are so-answered.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 52-55, 57, 58, 61-64, and 69-73 remain rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 6,395,549 to Tuan, et al., Recillas-Targa, et al. (2002) Proceedings of the National Academy of Sciences, USA, 99(10) 6883-88), Chung, et al. (1997) Proceedings of the National Academy of Sciences, USA, 94: 575-80, and U.S. Patent No. 6,432,700 to Henderson, et al. as applied to claims 52-55, 57, 58, 62-64, and 69-73 above, and further in view of U.S. Patent No. 6,194,152 to Laus, et al., for reasons of record.

As shown above, the Art teaches various claims, but does not teach the transgene for expressing thymidine kinase.

On the other hand, Laus teaches expression of thymidine kinase transgenes as a selectable marker in mammalian cells (e.g., section titled "c. Expression in Mammalian Systems", paragraph 7).

Hence, it would be further obvious to modify the vectors to comprise the thymidine kinase transgene as a marker for mammalian cell expression. Moreover, the Artisan would have a reasonable expectation of success, as such markers were well known in the Art.

***Response to Argument – 103 – Tuan/Recillas-Targa/Chung/Henderson/Laus***

Applicant's arguments rely on the base argument above, and are so-answered.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

Art Unit: 1633

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 52-58, 62-66, and 68-74 remain rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 6,395,549 to Tuan, et al., Recillas-Targa, et al. (2002) Proceedings of the National Academy of Sciences, USA, 99(10) 6883-88), Chung, et al. (1997) Proceedings of the National Academy of Sciences, USA, 94: 575-80, and U.S. Patent No. 6,432,700 to Henderson, et al. as applied to claims 52-55, 57, 58, 62-64, and 69-73 above, and further in view of U.S. Patent No. 6,113,898 to Anderson, et al. and Aldrich, et al. (1998) Cytotechnology, 28: 9-17, for reasons of record.

As shown above, the Art teaches various claims, but does not teach the use of CHO cells, or the expression of the heavy and light chains of an immunoglobulin nor the use of bicistronic vectors, or humanized sequences.

On the other hand, Anderson teaches CHO cells being transformed to express the heavy and light chains of antibodies to the human B7.1 and/or B7.2 antigens (e.g., Summary of the Invention, penultimate paragraph).

Aldrich teaches the use of bicistronic vectors for expression, which provide for reducing the time required to develop cell pools for protein expression (e.g., ABSTRACT).

Moreover, the Artisan would isolate the Immunoglobulin for use (Official Notice).

Hence, at the time of invention, it would have been obvious to further modify the vector to comprise the coding sequences of the heavy and light chains of such antibodies in a bicistronic vector of aldrich. The Artisan would do so in order to express such in CHO cells, isolate the

proteins, and reduce the time to develop cell pools for protein expression. Moreover, there is a reasonable expectation of success, as Anderson teaches such expression.

***Response to Argument – 103 – Tuan/Recillas-Targa/Chung/Henderson/Anderson/Aldrich***

Applicant's arguments rely on the base argument above, and are so-answered.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 52-58, 60, 62-66, and 68-74 remain rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 6,395,549 to Tuan, et al., Recillas-Targa, et al. (2002) Proceedings of the National Academy of Sciences, USA, 99(10) 6883-88), Chung, et al. (1997) Proceedings of the National Academy of Sciences, USA, 94: 575-80, and U.S. Patent No. 6,432,700 to Henderson, et al.; U.S. Patent No. 6,113,898 to Anderson, et al. and Aldrich, et al. (1998) Cytotechnology, 28: 9-17 as applied to claims 52-58, 62-66, and 68-74 above, and further in view of U.S. Patent No. 6,632,927 to Adair, et al.

As shown above, the various aspects are obvious, except the use of humanized sequences for a chain of the antibody.

On the other hand, Adair teaches humanized antibody sequences for expression in cells (e.g., ABSTRACT).

Hence, it would be obvious to substitute Adair's humanized sequences. The Artisan would do so to produce the humanized antibodies taught by Adair. Moreover, the Artisan would have a reasonable expectation of success, as Adair teaches such.

***Response to Argument – 103 – Tuan/Recillas-***

***Targa/Chung/Henderson/Anderson/Aldrich/Adair***

Applicant's arguments rely on the base argument above, and are so-answered.

***Conclusion***

No Claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ROBERT M. KELLY whose telephone number is (571)272-0729. The examiner can normally be reached on M-F, 9:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Weitach can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Robert M Kelly/  
Primary Examiner, Art Unit 1633